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(54) Title: DRUG FOR TREATING AFFECTIONS RELATED TO AN UNDESIRABLE HISTAMINE LEVEL, OF THE GASTRODUODENAL MUCOSA AND ALLERGIC AFFECTIONS (57) Abstract Drug for treating affections provoked by a too high histamine level in the body, for treating affections of the gastroduodenal mucosa and allergic affections, comprising the reaction product of (+) -catechin with at least one basic amino-acid, which is more particularly selected from the group consisting of L-lysine, L-arginine and L-ornithine.		

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Drug for treating affections related to an undesirable histamine level, of the gastroduodenal mucosa and allergic affections.

5 This invention relates to a drug and a method for treating affections related to an undesirable histamine level in the body or to an undesirable high histamine release in the body, affections of the gastroduodenal mucosa and allergic affections.

According to the invention the drug comprises the reaction product of (+) -catechin with at least one basic amino-acid.

10 According to a particular embodiment of the invention, said drug comprises the reaction product of (+) -catechin with said basic amino-acid and further at least one other organic or inorganic acid.

15 The amino-acid may be natural or not, such as, for example, lysine, arginine, ornithine, L-lysine, L-arginine and L-ornithine.

20 The inorganic acids may be, for example, hydrochloric acid, sulfuric acid or phosphoric acid and the organic acids may be aliphatic, cycloaliphatic, aromatic, araliphatic or heterocyclic carboxylic or sulphonic acids, such as, for example, acetic, propionic, glycolic, gluconic, lactic, tartaric, citric, ascorbic, glucuronic, glutamic, methanesulfonic, toluenesulfonic, malonic, galactaric, galacturonic, maleic, fumaric acids.

25 Based on new biochemical and pharmacological observations, it has been found that said reaction products

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of (+) -catechin and at least one basic amino-acid, and of (+) -catechin, one basic amino-acid and at least another organic or inorganic acid, are able to lower the histamine level in various tissues and cells, including gastric mucosa mast cells, peritoneal mast cells, leucocytes and lung tissue, and to inhibit the histamine release from mast cells.

It is known that the histamine present in human gastric mucosa is exclusively localized in the mastocyte cells and that said histamine has an important effect on the secretion of gastric acid and on the origin of gastroduodenal ulcers (K. Mohri, e.a., Agents and Actions, 8, 372, 1978).

Furthermore, it is well known that histamin release caused by allergens plays a major role in allergic affections.

Consequently, the above mentioned reaction products of (+) -catechin present great pharmaceutical interest for the treatment of gastroduodenal ulcers and affections of the gastric mucosa, of gastro-intestinal allergy and of allergic affections of the skin and of the respiratory system.

Of particular interest for said treatments are reaction products of (+) -catechin and L-lysine or L-arginine and of (+) -catechin and L-lysine or L-arginine and a mineral acid, such as hydrochloric acid, or an organic acid, such as acetic acid, citric acid or ascorbic acid.

Examples of said (+) -catechin derivatives which are particularly interesting are :

(+) -catechin hydrochloralysinate
(code number CP 1850 FL)

(+) -catechin ascorbolysinate (code
number CP 1939 FL)

(+) -catechin lysinate.

The newly discovered pharmaceutical properties of said (+) -catechin derivatives have been proved by several studies in vitro, on animal models and on human beings, which

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are summarized hereafter.

Biochemical studies in vitro have indicated that (+) -catechin hydrochlorolysinate inhibits histidine decarboxylase extracted from rabbit stomach with an IC_{50} of 10^{-4} M.

5 Further studies, carried out in vitro, have shown that the release of histamine from rat peritoneal mastocytes, stimulated by the release inducer 48/80, is inhibited by (+) -catechin hydrochlorolysinate by 27% at a concentration of 10^{-5} M.

10 The amount of released histamine has been measured after incubation of the cells at 37°C during 10 minutes with either an amount of compound 48/80 determined to obtain a release of 50%, either with such quantity of compound 48/80 in combination with the test substance.

15 The inhibiting activity of said (+) -catechin derivatives on histamine release from rat peritoneal mastocytes has been confirmed by ex vivo studies. In these experiments the inhibiting effect of CP 1850 FL on the histamine release induced by compound 48/80 in Sprague-Dawley rat peritoneal mast cells was studied. Sodium cromoglycate was used as a standard. The drugs tested
20 were administered orally (suspended in 1% carboxymethylcellulose) during 3 days, 3 times a day at a dose of 30 mg/kg.

The mast cells were obtained after sacrifice by i.p. injection of Hank's balanced salt solution (HBSS) ; a gentle massage of the abdomen was applied, the peritoneal fluid
25 was collected, centrifuged and the cell pellet resuspended in HBSS.

The mast cells were then incubated during 10 minutes at 37°C in the presence of an amount of compound 48/80, in HBSS, adjusted to obtain 50% histamine release in the control group. The cells and the supernatant were recovered by centrifugation
30 and the histamine in the cell pellet and in the supernatant is determined by an automatic procedure (Technicon All).

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Compared to the controls the histamine release of the mast cells of the CP 1850 FL-treated group was decreased by 22 % and of the cromoglycate-treated group by 3%.

5 The effect of CP 1850 FL was statistically significant whether sodium cromoglycate was inactive in these conditions.

Sodium cromoglycate is a generally accepted anti-allergen which is in particular used in the treatment of allergic disorders of the respiratory system [E.G. Weinberg et al.,
10 SA Medical Journal, 64, 896-899 (1983)].- Usually the drug is administered in the form of an aerosol, because administering per os gives poor results. One of its modes of action is believed to be its inhibiting effect on the histamine release from mast cells [J. Bernstein, J. Allergy Clin. Immunol., 68, 247-253 (1981)].

15 Further studies, made in vivo, indicated that intraperitoneal injection of (+) -catechin hydrochlorolysinate at 30 mg/kg, induces a decrease of 33% of the histamine content in rat stomach mucosa and of 38% in the lungs.

The effect of the (+) -catechin derivatives on the histamine content of stomach mucosa has been confirmed
20 by clinical studies on human beings.

In this study, 4 groups of 10 healthy persons received per os in double blind either placebo, either 500 mg, 1000 mg or 1500 mg of (+) -catechin hydrochlorolysinate per day during
25 3 days. Biopsies were taken before and after the treatment. In the treated groups, a decrease of the histamine level of the mucosa of the fundus, of the corpus and of the antrum has been observed which is dose dependant and which reaches a 30% decrease at the highest dose. The number of mastocytes has decreased in the same way.
30 In the placebo group, the histamine level remained constant in the three areas of the stomach.

Taking into account the histamine release inhibiting properties of said reaction products of (+) -catechin

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and a basic amino-acid and the known effect of histamine on the genesis of gastric ulcers, it was expected that the amino-acid derivatives of (+) -catechin present beneficial effects for the treatment of affections of the gastroduodenal mucosa.

5 The preventive and curative effect of said (+) -catechin derivatives has clearly been proved by studies on animal models, which are summarized here after.

The preventive effect of (+) -catechin hydrochlorolysinate and of (+) -catechin ascorbolysinate has been studied
10 as follows :

a) on ulcers induced by stress provoked by immobilisation :

After one week adaptation to the environment, female rats (30 animals per group, 5 per cage) were immobilised during 12 hours by wrapping them, under narcosis with ether, in a plaster bandage.

15 After sacrifice of the animals, the dissected stomach was visually inspected and the lesions of the mucosa were scored according to their number and their intensity.

b) on ulcers induced by stress provoked by cold :

The experimental conditions are the same as the ones used in the
20 study of ulcers induced by immobilisation, but in this model, stress was induced by placing the rats, one per cage, in a cold room at -10°C for 5 hours.

The products to be tested were administered, immediately before the test, by intraperitoneal injection
25 of 2 ml of a freshly prepared saline solution. The doses tested varied from 0.1 to 50 mg/kg. The controls received 2 ml of saline.

The results obtained in a comparative study showed that treatment with the (+) -catechin reaction products and with (+) -catechin induced
30 a significant and dose dependant decrease in the number of lesions of the stomach of stressed rats.

The results obtained show that the effective dose, providing protection against gastric ulcers to 50 % of the animals (ED50 value) is for

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for CP 1939 FL : 3.5 mg/kg
for CP 1850 FL : 8.0 mg/kg
for (+) -catechin : 15.0 mg/kg.

5 When expressed in terms of anhydrous (+) -catechin, this is the amount of anhydrous (+) -catechin corresponding to the stoichiometric amount of anhydrous catechin involved in the (+) -catechin reaction product, the ED50 values are as follows :

- 10 - for CP 1939 FL : 1.5 mg/kg
- for CP 1850 FL : 5.0 mg/kg
- for (+) -catechin : 13.5 mg/kg.

Similar results were obtained against cold induced ulcers in rats and guinea-pigs.

15 Furthermore, the preventive action of the catechin derivatives against stress induced gastric ulcers has been shown also after their administration by oral route.

The technique used consisted of oral administration to rats of 30 mg/kg of (+) -catechin hydrochlorolysinate, given as a suspension in a 1% aqueous solution of carboxymethyl-cellulose. The tested product was given 3 times a day during the 20 3 days preceding the experiment. The last administration was given 1 hour before immobilisation of the rats during 12 hours.

25 After sacrifice, inspection of the gastric mucosa revealed a significant decrease of the proportion of rats with severe lesions : from 38% for the control group to 15% for the treated group.

The curative activity on gastro-duodenal mucosa of the amino-acid derivatives of (+) -catechin has been established on animal models by means of the following technique:

a. On necrosis induced by acetic acid.

30 In rats fasted for 24 hours, necrosis of the gastric mucosa was induced by intra-gastric administration

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of of acetic acid (1 ml at 20%) one hour before treatment.

As a suspension in an aqueous solution of 1% carboxymethylcellulose, (+) -catechin hydrochlorolysinate was administered orally twice a day during 5 days.

5 Accordingly the rats were sacrificed, the stomach mucosa was photographed and the lesions were scored.

In these conditions, at a dose of 150 mg/kg, a significant curative effect was noted as a reduction of 50% of the number of animals with severe lesions.

10 b. On erosion induced by N-acetylcysteine.

N-acetylcysteine provokes a mucus dissolution by breaking off the S-S-links of mucus glycoproteins. After repeated treatment by N-acetylcysteine (100 mg/kg p.o. every 15 minutes during 1 hour) the stomach of the control animals (Sprague Dawley rats) losted 70% of the mucus
15 [determined colorimetrically after Alcian blue coloration, according to a method described by S.J. Korne et al., J. Physiol., 242, 116-117 (1974)].

In a dose-effect study, CP 1850 FL was administered once orally at 0.01, 0.1, 1, 10, 30 and 100 mg/kg to Sprague Dawley rats, 1 hour
20 before treatment with N-acetylcysteine (100 mg/kg p.o., every 15 minutes during 1 hour).

The results obtained are the following :

25 Dose of CP 1850 FL (mg/kg)	Remaining mucus (µg Alcian blue/g tissue) after mucolysis by N-acetylcysteine [means \pm SEM] (n = 8)
-	39 \pm 1.9
0.01	35 \pm 2.4
0.1	38 \pm 2.0
1	40 \pm 1.4
10	44 \pm 2.4
30	50 \pm 4.5 *
100	56 \pm 4.8 **

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Statistical analysis of the results was performed with anova and followed by Dunnett's t test. The significant differences with the control are indicated as follows :

x significant at level $p < 0.05$

5 xx significant at level $p < 0.01$

These results show a protective effect of (+) -catechin hydrochlorolysinate which is significant from a dose of 30 mg/kg.

In the same test conditions, the same results have been obtained when CP 1850 FL has been administered (30 mg/kg) either orally, either
10 intraperitoneally.

c. On erosion induced by acetylsalicylic acid.

Acetylsalicylic acid (ASA) is well known to induce erosion of the gastric mucosa. To Sprague Dawley rats fasted for 18 hours, CP 1850 FL in a 1 % carboxymethylcellulose (CMC) suspension, has been administered orally during 3 days, 3 times a day, and one more administration
15 was given 1 hour before treatment with ASA (100 mg/kg, p.o.).

The animals were sacrificed 4 hours after treatment with ASA, the stomach was removed, incised along the greater curvature and the degree of erosion of the mucosa in the glandular part was estimated
20 by a scoring system designed by Marrazzi-Uberti and Turba [Med. Exp. 4, 284 (1961)].

0 = no erosion

1 = 1-3 small erosions (4 mm or smaller)

25 2 = more than 3 small erosions or one large erosion

3 = one large erosion and more than 3 small erosions

4 = 3-4 large erosions

30 5 = many large erosions or ulcer-perforation

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The doses tested varied from 30 mg/kg to 300 mg/kg and the controls received only the vehicle (CMC).

The following result have been obtained :

5	Drugs administered		Score (means \pm SEM) (n = 10)
	CP 1850 FL mg/kg	Acetylsalicylic acid mg/kg	
	-	-	0.2 \pm 0.1
	-	100	2.7 \pm 0.6
	30	100	1.6 \pm 0.4
10	100	100	1.3 \pm 0.4 x
	300	100	1.0 \pm 0.3 x

One way variance analysis, Dunnett's t test.

x significant at level $p < 0.05$

15 These results clearly indicate the inhibiting effect of CP 1850 FL against erosion of the gastric mucosa induced by ASA.

20 The lowering effect on the histamine level of the gastric mucosa and the curative activity on gastroduodenal ulcers of (+) -catechin hydrochlorolysinate have been confirmed in human beings in a double blind study, in which the aminoacid derivative of (+) -catechin has been compared to cimetidine.

25 Patients suffering from duodenal ulcer were treated daily either with 1500 mg (+) -catechin hydrochlorolysinate (11 patients) either with 800 mg cimetidine (10 patients) during 4 weeks. Photographs of the ulcer and biopsies of the stomach mucosa were taken before and after each week of treatment.

The results obtained with (+) -catechin hydrochlorolysinate confirmed the activity observed previously, since

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a decrease of the histamine levels and a decrease of the number of mastocytes in the fundus, corpus and antrum mucosa by + 20 % has been measured. Also a decrease of the main histamine level of the plasma from 0.7 (+ 0.3) ng/ml to 0.3 (+ 0.1) ng/ml has been observed.
5 The decrease was observed after one week treatment and remained constant during the following 3 weeks of the treatment.

(+) -catechin hydrochlorolysinate has no effect on the intragastric pH.

In the other group cimetidine showed
10 no notable effect or induced an increase, in some cases of more than 10% of the histamine levels in the stomach mucosa and in the plasma.

Further results, based on the measurements of the ulcer diameter, confirmed the curative properties of (+) -catechin hydrochlorolysinate on human duodenal ulcer : 7 patients out of 11 had fully recovered after 1 month of treatment.
15 The ulcer diameter of the other patients had decreased significantly.

In further biochemical studies carried out in vitro it was found that amino-acid derivatives of (+) -catechin are effective inhibitors of antigen induced histamin release from leucocytes of persons who are sensitive to allergic affections provoked by pollen or house dust.
20

This activity of the catechin derivatives has clearly been established by the following technique : the leucocytes, preincubated during 10 minutes at 37°C with hydrochlorolysinate of (+) -catechin, were treated with the allergen, pollen or house dust, during 30 minutes at 37°C to activate the histamine release.
25

Then the histamin level was measured in the leucocyte suspension and the supernatant liquid and compared to the values obtained from the controls. Preincubation of the leucocytes by 10^{-5} M or 10^{-6} M hydrochlorolysinate of (+) -catechin resulted in a release inhibition of 45%.
30

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The effect of (+) -catechin hydrochloro-lysinate (CP 1850 FL) on allergen induced gastric ulcer has been evidenced by in vivo tests carried out on the African rodent *Praomys* (*Mastomys*). Said animal has a special system of histamine storing enterochromaffin-like cells at the level of the gastric mucosa. Animals were sensitized with one intraperitoneal injection of 3 µg of ovalbumin dissolved in 0.2 ml of saline containing 1 mg aluminium hydroxide. The sensitized animals developed only IgE and IgG₁ reagenic antibodies. Seven days later, 1 mg of ovalbumin in 0.01 ml saline was injected intra-mucosally in the corpus region of the stomach. This injection resulted in the appearance 72 h later of a single gastric ulcer at the challenge site. The ulcer appeared as a round lesion, the larger ones reaching a size of 6 mm. This anaphylactic ulcer in the *mastomys* is very similar to that of a peptic ulceration in humans (F. André et al., *Amer. J. Pathol.*, 102, 133 (1981). CP 1850 FL, 300 mg/kg administered orally twice a day (2 days before the last injection of ovalbumin and during 5 days), decreases significantly the number of animals with ulcer from 23/24 (controls) to 5/12 (treated). At 10, 30 and 100 mg/kg p.o. in the same conditions the number of animals with ulcer decreased but not significantly (respectively 9/12, 8/12 and 9/12). At 100 mg/kg i.p. a significant protection is also noted. At 100 mg/kg i.p. and at 300 mg/kg p.o. the decrease of the histamine level in the stomach is significant (see tables 1 and 2, pages 12 and 13). The results show clearly the inhibiting effect of CP 1850 FL on allergen induced gastric ulcer and the correlation between this effect and the decrease of the gastric histamine level.

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Table 1.INCIDENCE AND SEVERITY OF ANAPHYLACTIC ULCER IN MASTOMYS.

Treatments	Number of animals	Number of ulcerous animals	Severity score means \pm SEM
NaCl 0.15 M p.o.	24	23	1.8 \pm 0.4
CP 1850 FL 10 mg/kg p.o.	12	9	2.2 \pm 0.3
CP 1850 FL 30 mg/kg p.o.	12	8	2.1 \pm 0.3
CP 1850 FL 100 mg/kg p.o.	12	9	2.4 \pm 0.2
CP 1850 FL 300 mg/kg p.o.	12	5 ***	1.2 \pm 0.2
CP 1850 FL 100 mg/kg i.p.	12	6 ***	1.6 \pm 0.2

*** p < 0.01 Chi 2 corrected.

**** p < 0.001 Chi 2 corrected.

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Table 2.

HISTAMINE LEVEL AND NUMBER OF MASTOCYTES IN THE FUNDUS MUCOSA OF MASTOMYS.

Treatments	Number of animals	Histamine 10 ⁻⁶ mg/kg prot. (means \pm SEM)	Mucous mastocytes (means \pm SEM)	Serous mastocytes (means \pm SEM)	Total mastocytes (means \pm SEM)
NaCl 0.15 M p.o.	12	46.17 \pm 2.30	21 \pm 2	110 \pm 14	131 \pm 15
CP 1850 FL 10 mg/kg p.o.	12	47.29 \pm 4.78	24 \pm 5	106 \pm 8	130 \pm 10
CP 1850 FL 30 mg/kg p.o.	12	51.08 \pm 3.56	22 \pm 4	97 \pm 8	119 \pm 9
CP 1850 FL 100 mg/kg p.o.	12	40.28 \pm 3.08	25 \pm 4	103 \pm 13	128 \pm 16
CP 1850 FL 300 mg/kg p.o.	12	37.91 \pm 3.73	16 \pm 3	79 \pm 10	95 \pm 13
CP 1850 FL 100 mg/kg i.p.	12	34.98 \pm 3.52	26 \pm 8	97 \pm 14	123 \pm 20

* p < 0.05 t Student

*** p < 0.01 t Student

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The activity of amino-acid derivatives of (+) -catechin on the histamine level of lung tissue is shown by the following experiment : two groups of 10 female Sprague-Dawley rats received either placebo either 30 mg/kg (+) -catechin hydrochlorolysinate during 3 days, 3 times a day. The drug was administered per os as a suspension in carboxymethyl cellulose (1% in water). Five hours after the last treatment the rats were sacrificed and the histamine level in the homogenized lung tissue has been determined. In the treated group a decrease of the histamine level of 38% compared to the control group has been measured.

Toxicological studies have shown that the considered amino-acid derivatives of (+) -catechin have extremely low toxicity.

The acute toxicity of (+) - catechin hydrochlorolysinate, administered per os in rat is over 6 g/kg in both sexes. No mortality was found up to this dose, which did not cause behavioural changes.

Subacute toxicity studies in rat and in Cynomolgus monkeys indicated that (+) -catechin hydrochlorolysinate is well tolerated at doses up to 1000 mg/kg administered daily and per os during 5 weeks to monkeys and during 6 weeks to rats.

Besides, (+) -catechin hydrochlorolysinate is free of mutagenic properties, as is proven by the results of the Ames test and by the absence of chromosomic aberrations on human lymphocytes in vitro.

The experimental results given above clearly demonstrate that the amino-acid derivatives of (+) -catechin, specified previously, exhibit important protective and curative activities on lesions of gastroduodenal mucosa and anti-allergic properties since they are able to lower the histamine content in various tissues and to decrease the histamine release from various cells.

Consequently, said compounds have great therapeutical value for the treatment of gastroduodenal ulcers

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and for the treatment of allergic affections of the respiratory system, such as asthma and rhinitis, of allergic affections of the skin, such as contact dermatitis and urticaria, of gastro-intestinal allergy and of allied allergic diseases.

5 The catechin derivatives useful for this invention may be administered, in view of the intended therapeutical application, orally, parenterally, topically, rectally or as an aerosol in various galenic forms.

10 This comprises pharmaceutical compositions containing as active ingredient at least a minimal effective amount of at least one of said reaction products of (+) -catechin and L-lysine, L-arginine or L-ornithine and which may contain also diluents, carriers or excipients and/or pharmaceutical active ingredients.

15 Thus for example the compositions to be administered orally can be liquids or solids and exist as tablets, sugar-coated pills, coated tablets, capsules, granules, powders, syrups or suspensions. The dry oral formulations comprise additives and excipients usually used in galenic pharmacy, inert diluents, desintegration agents, binders and lubricants, such as lactose, starch, talc, gelatin,
20 stearic acid, cellulose and derivatives thereof, silicic acid, magnesium stearate, polyvinylpyrrolidone, calcium phosphate, calcium carbonate and the like.

The aqueous suspensions, the emulsions and the oily solutions are prepared in the presence of sweetening agents, such as dextrose or glycerol, flavouring agents, such as vanillin
25 for example, and can also contain thickening agents, wetting agents, preservation agents.

The oily emulsions and solutions are prepared in an oil of vegetal or animal origin and can contain emulsifiers, flavouring, dispersing, sweetening and antioxidant agents. For
30 parenteral administration, sterile water, an aqueous polyvinylpyrrolidone solution, peanut oil, ethyl oleate and the like are used as a vehicle.

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These aqueous or oily injectable solutions can contain thickening, wetting, dispersing and gelling agents.

For rectal administration, several galenic forms can be used such as suppositories or rectal capsules or gels.

5 The catechin derivatives useful for treating and preventing gastroduodenal and allergic affections can be used alone or in combination with other pharmaceutical active compounds exerting a similar or a different activity.

Usual daily doses for oral and rectal administration of the (+) -catechin derivatives, may vary from 200 mg to 5 g, and are preferentially 1500 mg. Usual daily doses for parenteral administration of the (+) -catechin derivatives vary from 50 mg to 5 g and are preferentially 1500 mg.

15 For topical administration galenic forms such as, for example, creams, pastes, ointments, solutions, suspensions, emulsions or gels can be used and the usual concentration compound in said galenic forms may vary from 0.1% to 30%.

Hereafter, a few galenic formulations are described as non limitative examples in which the active compound is represented by A and is chosen from the following compounds :

20 (+) -catechin hydrochlorolysinate
(+) - catechin ascorbolysinate
(+) -catechin lysinate.

Tablets

25	A	500 mg
	Ac-Di-Sol	90 mg
	Aerosil 200	20 mg
	Polyvinylpyrrolidone	30 mg
	Talc	30 mg

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	A	200 mg
	Aerosil 200	12 mg
	Talc	12 mg
	Ac-Di-Sol	35 mg
5	Magnesium stearate	1 mg

Suppositories

	A	500 mg
	Witepsol H 15	2500 mg

Injectable

10	A	20 mg
	Benzylalcohol	20 mg
	Lysine	ad pH = 7.4
	aqua purificata	ad 1 ml.

Cream

15	A	10 mg
	Glycerin	2 g
	Perhydrosqualene	8 g
	Liquid paraffin	8 g
	Solid paraffin	6 g
20	Cetylstearyl alcohol	4.5 g
	Sodium cetylstearylsulfate	0.5 g
	Emulgin B-3	2 g
	Aluminium stearate	0.3 g
	Citric acid	0.1 g
25	Nipasept	0.2 g
	Distilled water	ad 100 g

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It has to be noted that the studies and tests referred to hereinabove are also valid for drugs comprising the reaction products of (+) -catechin with L-arginine or L-ornithine and optionally combined with another acid as defined hereinabove.

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CLAIMS

1. Drug for treating affections related to an undesirable high histamine level or to an undesirable high histamine release in the body, for treating affections of the gastroduodenal mucosa and allergic affections, comprising the reaction product of (+) -catechin with at least one basic amino-acid.
2. Drug according to claim 1, wherein the basic amino-acid is selected from the group consisting of L-lysine, L-arginine and L-ornithine.
3. Drug according to claim 1 or 2, comprising the reaction product of (+) -catechin with said basic amino-acid and further at least one other organic or inorganic acid.
4. Drug according to claim 3, wherein said other acid is selected from the group consisting of hydrochloric acid, acetic acid, citric acid and ascorbic acid.
5. Drug according to anyone of claims 1 to 4, wherein said reaction product is in association with at least one suitable excipient.
6. Drug according to claim 5, being in the form of a solution or an aerosol.
7. Drug according to claim 5, being in the form of an ointment or a cream.
8. Drug according to claim 5, being in the form of suppositories.
9. Drug according to claim 5, being in the form of tablets.
10. Drug according to anyone of claims 1 to 9 for treating gastroduodenal ulcer.
11. Drug according to anyone of claims 1 to 9 for treating gastro-intestinal allergy.
12. Drug according to anyone of claims 1 to 9 for treating allergic affections of the respiratory system.

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13. Drug according to anyone of claims 1 to 9 for treating allergic affections of the skin, allergic contact dermatitis and urticaria.

5 14. A method for treating disorders related to an undesirable high histamine level or to an undesirable high histamine release in the body, for treating affections of the gastroduodenal mucosa, for treating gastroduodenal ulcer and for treating allergic affections, which comprises administering to a host in need for such treatment an effective amount to produce a curative or preventive effect, of the reaction product of (+) -catechin with at least
10 one basic amino-acid and optionally with another acid.

15 15. A method as claimed in claim 14, wherein the basic amino-acid is selected from the group consisting of L-lysine, L-arginine and L-ornithine.

16. A method as claimed in claim 14 wherein said other acid is selected from the group consisting of hydrochloric acid, acetic acid, citric acid and ascorbic acid.

17. A method as claimed in claim 14 wherein the basic amino-acid is L-lysine and said other acid is
20 hydrochloric or ascorbic acid.

18. A method as claimed in one of claims 14 to 17 for treating lesions of the gastroduodenal mucosa.

19. A method as claimed in one of claims 14 to 17 for treating gastroduodenal ulcers.

20. A method as claimed in one of claims 14 to 17 for treating allergic affections.

21. A method as claimed in one of claims 14 to 17 for treating allergic affections of the gastroduodenal mucosa or of allergic gastroduodenal ulcers.

22. A method as claimed in one of claims 14 to 17 for treating allergic affections of the respiratory system.

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23. A method as claimed in one of claims 14 to 17 for treating allergic affections of the skin.

5 24. A method as claimed in one of claims 14 to 23 comprising administering said (+) -catechin reaction product orally, rectally, parenterally, topically or as an aerosol at a daily dose of 50 mg to 5 mg, preferably orally or rectally at a daily dose of 200 mg to 5 g or parenterally at a daily dose of 50 mg to 5 g.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/BE 84/00019

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁴ : A 61 K 31/35; A 61 K 9/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
IPC ⁴	A 61 K 31/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁴ .		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁵	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X,Y	BE, A, 886568 (CONTINENTAL PHARMA) 9 June 1981 see pages 1-3, page 9, lines 30-33; claims	1-12
X,Y	GB, A, 2057437 (CONTINENTAL PHARMA) 1 April 1981 see pages 1-4	1-13
Y	FR, A, 2128207 (ZYMA) 20 October 1972 see pages 1,2,4	1,5-11
Y	Chemical Abstracts, vol. 92, 1980 (Columbus, Ohio, US) S. Ramaswamy et al.: "The antihistaminic activity of (+)-cyanidan-3-ol-on isolated guinea pig ileum", see page 34, abstract no. 15315e, & Indian J. Pharmacol. 1979, 11(2), 135-8 (Eng.)	1,5-11
A	Chemical Abstracts, vol. 93, 1980 (Columbus, Ohio, US) C.N. Rao et al. "Effect of bioflavonoids on the	./.
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹³</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the International filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the International filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ³	
19th October 1984	15 NOV. 1984	
International Searching Authority ¹	Signature of Authorized Officer ¹⁰	
EUROPEAN PATENT OFFICE	G.L.M. Kruydenburg	

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

urinary excretion of hydroxyproline, hydroxylysyl glycosides and hexosamine in adjuvant arthritis", see page 53, abstract no. 161201b, & Ital. J. Biochem. 1980, 29(2), 89-101 (Eng.)

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V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 14-24 because they relate to subject matter ¹¹ not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (see PCT Rule 39/1(iv)).

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹², specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹³

This international Searching Authority found multiple inventions in this international application as follows:

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1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/11/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE-A- 886568	09/06/81	None	
GB-A- 2057437	01/04/81	BE-A- 884743	01/12/80
		FR-A,B 2464262	06/03/81
		DE-A- 3031710	12/03/81
		NL-A- 8004873	03/03/81
		JP-A- 56055386	15/05/81
		US-A- 4285964	25/08/81
		SE-A- 8005890	01/03/81
		AT-B- 372381	26/09/83
		CA-A- 1172259	07/08/84
		JP-A- 59144779	18/08/84
FR-A- 2128207	20/10/72	DE-A,B,C 2206570	21/09/72
		GB-A- 1341794	25/12/73

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